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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/821,335
Filing Date: April 09, 2004
Appellant(s): WIGHTMAN ET AL.

Ted K. Ringsred
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/5/09 appealing from the Office action mailed 1/27/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

Claims 6-9, 13 have been canceled.

This appeal involves claims 1,3,11,12 and 14.

Claims 10, 15-51 are withdrawn from consideration as not directed to the elected invention.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

7030129	Miller et al	4/18/09
4689338	Gerster et al	8/1987
6894060	Slade	5/2005
7427620	Kedl Ross et la	8/2008
5078978	Tarbet	1/1992

Robert Langer New Methods of Drug Delivery , 1990.

WO 2001/023067, Ronald et al , May 2001.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The rejection of the claims under 35 USC 112 scope of enablement has been withdrawn .

The rejection of the claims under 35 USC 102 has been withdrawn as applicants complexes are covalently bonded to the macromolecules and not just admixed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 11, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller US 7,030,129, Gerster US 4,689,338 , Slade US 6.894,060 in view of Langer et al 1990 New Methods of Drug Discovery.

Appellants' claims are drawn to an IRM compound which is covalently bonded to a macromolecular support.

The IRM compound is drawn to several compounds which are amines and have a core selected from the group consisting of imidazoquinoline amines; tetrahydroimidazoquinoline amines; and imidazopyridine amines; 1,2-bridgedimidazoquinoline amines; 6,7-fusedcycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines. These comprise several thousand compounds as long as they have this core.

A **covalent bond** is a form of chemical bonding that is characterized by the sharing of pairs of electrons between atoms, or between atoms and other covalent bonds. In short, attraction-to-repulsion stability that forms between atoms when they share electrons is known as covalent bonding.[1].

The claims read on a IRM which is covalently bonded to a macromolecular support. The dependent claims specifically give the different macromolecular supports.

Scope & Content of Prior Art MPEP 2141.01

Miller, Gerster , Slade all disclose various IRMs which fall within the scope of applicants compounds. These are also used for cytokine induction and to treat viral and neoplastic disorders.

TLR6 is used to treat neoplastic disorders.

Langer et al teaches using drugs covalently bonded on macromolecules e.g polymers which are used for drug delivery. Specifically, examples of antitumor agents is given.

Langer et al at Column 2 teaches that drugs can be attached to macromolecules such as a

research. Several experimental approaches have been developed, in which drugs are complexed to agents that enable them to cross this barrier (for example, by rendering the drug more lipophilic or coupling it to a molecule that has a specific transport mechanism) (1).

Drugs have also been attached to soluble macromolecules such as proteins, polysaccharides, or synthetic polymers via degradable linkages. This process alters the drug's size and other properties, resulting in different pharmacokinetics and biodistribution. One example involves coupling the antitumor agent neocarzinostatin to styrene–maleic acid copolymers (2). When this complex was injected intra-arterially into patients with hepatocellular carcinoma, decreases in α-fetoprotein levels and tumor size were observed. In animals, antitumor agents such as doxorubicin coupled to *N*-(2-hydroxypropyl) methacrylamide copolymers showed radically altered pharmacokinetics, resulting in reduced toxicity. The half-life of

polymer

Polymers, such as polyethylene glycol (PEG), can be attached to drugs to either lengthen their lifetime or alter their immunogenicity. The polymers physically prevent cells and enzymes from attacking the drug. PEG-uricase reduced serum urate levels in patients with hyperuricemia and gout; PEG-asparaginase has been used for patients with leukemia, and PEG–adenosine deaminase has been used for patients with a severe combined immunodeficiency (6). Drug longevity and immunogenicity may also be affected by biological approaches, including protein engineering and altering glycosylation patterns.

The reference also teaches the various motivations to use a drug complex: controlled release for drug delivery preservation of the medication that are rapidly destroyed, localized delivery , increased comfort, improved compliance, and reduced need for follow up care.

administration. Other potential advantages of controlled release systems include (i) localized delivery of the drug to a particular body compartment, thereby lowering the systemic drug level; (ii) preservation of medications that are rapidly destroyed by the body (this is particularly important for biologically sensitive molecules such as proteins); (iii) reduced need for follow-up care; (iv) increased comfort; and (v) improved compliance.

The reference also discusses degradable polymers, and also bioadhesive polymers (last line) column 1 of page 1532.
The covalently attached drug to a polymer is clearly taught. See section D.

The reference clearly also teaches altering the drug size and other properties to alter the drug properties such as enabling them to cross a barrier and not others. See column 2 page 1527.
Applicants own specification clearly states in the paragraph bridging pages 2 and 3 that the size should be such so as to prevent the penetration of the macromolecule into cells.

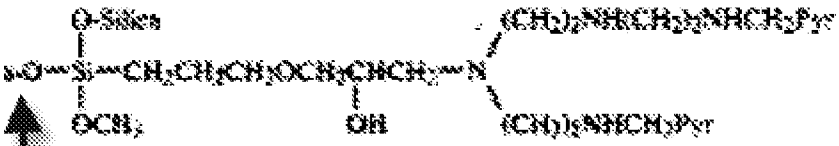
The examiner had also cited Tarbet US 5,078,978 and Ronald et al WO 2001/023067. These references were cited in response to the arguments made by the appellants in the response filed 10/21/08 in which they argued using the species they had made which had the Si solid support.

The claims no longer require those limitations and the rejected claims are obvious over the references cited in the statement of the rejection alone. However the reference also show the solid support in some of the complexes in the specifications.

US 5078978 Byron Tarbet et al which teaches various Si bonded spacers covalently bonding solid supports an compound which form a complex with the metal. It is active when it is still attached to the solid support.

10. A method according to claim 8 wherein the pyridine containing ligand covalently bonded to a solid inorganic support has the formula:

11. A method according to claim 8 wherein the pyridine containing ligand covalently bonded to a solid inorganic support has the formula:



12. A method according to claim 3 wherein the

portion of the compound is a reaction product of O-solid hydrophilic support material with a silicon containing spacer grouping selected from the group consisting of dimethyl(triethoxysilylpropyl)malonate; 3-mercapiopropyltrimethoxysilane; 3-aminopropyltrimethoxysilane; N-[(3-trimethoxysilyl)propyl]ethylenediaminetriacetic acid; p-(chloromethyl)phenyltrimethoxysilane; vinyltriethoxysilane; 3-bromopropyltriethoxysilane; 3-glycidoxypropyltrimethoxysilane; and combinations thereof.

Also see WO 2001/023067 Breuning Ronald, teaches ligands bonded covalently to s~ supports.

Difference between Prior Art and the claims MPEP 2141.02

The US patents Slade , Miller and Gerster teach the IRM compounds for the same use.

The Langler reference teaches the use of drug- macromolecular support complexes for drug delivery.
It meets the limitations of the polymers, PEG (in gels creams) and also the bioadhesives as macromolecules in the dependent claims. And also teaches why the size of the complex is increased so as to change the permeability.

WO 2001/023067 Breuning and US 5078978 Tarbet both teach using the the Si spacers and the Si support (meeting the limitations of the examples given in the specifications).

The difference is that the prior art does not teach the specific IRM-macromolecule complex.

Prima Facie Obviousness , Rational and Motivation MPEP 2142-2413

The US patents Slade , Miller and Gerster teach the IRM compounds for the same use.
The Langer reference teaches the use of drug- macromolecular support complexes for drug delivery. I t also teaches a cancer treating drug with is covalently bonded to a macromolecule.
WO 2001/023067 Breuning and US 5078978 Tarbet both teach using the Si spacers and the Si support
It would have been obvious to one of ordinary skill in the art of making compounds for drug delivery to use techniques as described in the Langer reference, of covalently bonding a drug to a macromolecular support in order to deliver it to the desired location or administration, in other words “targeting" drugs to specific cells. and would have been motivated to make the complexes from the IRM compounds with the macromolecular supports such as gels, polymers, bioadhesives and so on.

In view of KSR v Teleflex 2007, rationale it would certainly be obvious to try.
Appellants claims are broad and include any macromolecule and does not describe the spacer or the specific drug. See claim 1.
The claims are read in light of the specifications but the limitations of the specifications cannot be read into the claims..

When a work is available in one field of endeavor, design incentives and other mark forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictabl variation, 35 U.S.C. 103 bars its patentability

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." 31 "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." 32

Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." 33

The different rationals given in KSR are given by

Rationales

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try"—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

In this case it meets many of the rationales, A, E and F.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

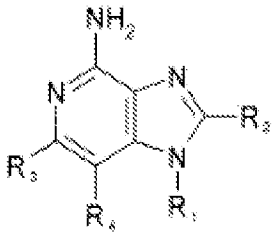
Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No.7,427,629. Although the conflicting claims are not identical, they are not patentably distinct from each other because

Appellants' claim is drawn to a complex of an IRM compound which is covalently bonded to a macromolecule.

The patent US '629 claim 1 is also drawn to the same IRM compound which is bonded to an antigen (macromolecule).

1. (Currently amended) An immunostimulatory composition comprising:

an immune response modifier portion of the formula:



and having IRM activity; and ~~covalently coupled to~~

a portion having antigenic activity that comprises;

an antigenic portion, or

a solid support to which an antigenic moiety is paired; [[,]]

wherein the immune response modifier portion is covalently coupled to the portion having antigenic activity through R_1, R_2, R_3, or R_4;

wherein the immune response modifier portion comprises an imidazoquinoline amine, a tetrahydroimidazoquinoline amine, an imidazopyridine amine, an aryl ether-substituted imidazopyridine amine, a 1,2-bridged imidazoquinoline amine, a 6,7-fused cycloalkylimidazopyridine amine, an imidazonaphthyridine amine, a tetrahydroimidazonaphthyridine amine, an oxazoloquinoline amine, a thiazoloquinoline amine, an oxazolopyridine amine, a thiazolopyridine amine, an oxazolonaphthyridine amine, or a thiazolonaphthyridine amine; and

(10) Response to Argument

Appellants argue that that Miller , Gerster and Slade do not disclose a complex. They say it is just mixed with the gel and cream. However, Langer teaches the convenience of drug delivery along with the example of other cancer agent clearly stating that the drug remains active when attached to the macromolecule.

Polymers, such as polyethylene glycol (PEG), can be attached to drugs to either lengthen their lifetime or aker their immunogenicity. The polymers physically prevent cells and enzymes from attacking the drug. PEG-uricase reduced serum urate levels in patients with hyperuricemia and gout; PEG-asparaginase has been used for

patients with leukemia, and PEG-adenosine deaminase has been used for patients with a severe combined immunodeficiency (6). Drug longevity and immunogenicity may also be affected by biological approaches, including protein engineering and altering

Appellants' claim as written is drawn to drug which is covalently bonded to a macromolecule , again the claims are read in light of the specifications but the limitations of the specifications cannot be read into the claims. Langer does teach the PEGylation, which is a covalent bond. See the following

Langer et al at Column 2 teaches that drugs can be attached to macromolecules such as a polymer

research. Several experimental approaches have been developed, in which drugs are complexed to agents that enable them to cross this barrier (for example, by rendering the drug more lipophilic or coupling it to a molecule that has a specific transport mechanism) (*1*).

Drugs have also been attached to soluble macromolecules such as proteins, polysaccharides, or synthetic polymers via degradable linkages. This process alters the drug's size and other properties, resulting in different pharmacokinetics and biodistribution. One example involves coupling the antitumor agent neocarzinostatin to styrene–maleic acid copolymers (*2*). When this complex was injected intra-arterially into patients with hepatocellular carcinoma, decreases in α-fetoprotein levels and tumor size were observed. In animals, antitumor agents such as doxorubicin coupled to *N*-(2-hydroxypropyl) methacrylamide copolymers showed radically altered pharmacokinetics, resulting in reduced toxicity. The half-life of

Polymers, such as polyethylene glycol (PEG), can be attached to drugs to either lengthen their lifetime or alter their immunogenicity. The polymers physically prevent cells and enzymes from attacking the drug. PEG-uricase reduced serum urate levels in patients with hyperuricemia and gout; PEG-asparaginase has been used for patients with leukemia, and PEG–adenosine deaminase has been used for patients with a severe combined immunodeficiency (*6*). Drug longevity and immunogenicity may also be affected by biological approaches, including protein engineering and altering glycosylation patterns

PEG is polyethylene glycol, found in creams and gels meeting the limitations of claims 3, 11 and 12 and 14 as it teaches discusses degradable polymers, and also bioadhesive polymers (last line) column 1 of page 1532.

Appellants argue that Langer does not suggest what type of drugs can be attached and what drugs are effective when conjugated, and in particular that Langer does not disclose the covalent attachment of IRM molecules to macromolecular supports. Appellants further argue that agents of Langer are not active until the linkage is cleaved, and it is surprising that appellant's molecules remain active while covalently bonded.

Applicants claim encompasses immune response modifiers attached to a macromolecular support , the support being further defined in claims 3, 11, 12 and 14, but they are not limited to non-cleavable supports nor do they require that the IRM s be active in the covalent form.

Besides Langer does clearly teach that the drug remains active even when it is covalently bonded . It just makes it more lipophilic or gives it it a transport mechanism.

> barrier (for example, by rendering the drug more lipophilic or coupling it to a molecule that has a specific transport mechanism)

It also keeps the drug active , see page 1529 of the Langer reference which states that a drug can be released for upto 5 yrs.

> **The use of polymers to deliver contraceptive steroids has been widely studied. Four types of systems have been examined: (i) subdermal reservoir implants composed of nondegradable polymers that release drug for over 5 years (for example, the Norplant); these**

Besides appellants' claims are just drawn to a complex of the IRM compounds which are covalently bonded to a macromolecular support. There is no limitation in the claim that they are active or that they remain active.

M.P.E.P. 2111.01 , ii II. IT IS IMPROPER TO IMPORT CLAIM LIMITATIONS FROM THE SPECIFICATION

"Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment." *Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004). See also *Liebel-Flarsheim Co. v. Medrad Inc.*, 358 F.3d 898, 906, 69 USPQ2d 1801, 1807 (Fed. Cir. 2004)(discussing recent cases wherein the court expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment);< *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) ("Interpretation of descriptive statements in a patent's written description is a difficult task, as an inherent tension exists as to whether a statement is a clear lexicographic definition or a description of a preferred embodiment. The problem is to interpret claims 'in view of the specification' without unnecessarily importing limitations from the specification into the claims."); *Altiris Inc. v. Symantec Corp.*, 318 F.3d 1363, 1371, 65 USPQ2d 1865, 1869-70 (Fed. Cir. 2003) (Although the specification discussed only a single embodiment, the court held that it was improper to read a specific order of steps into method claims where, as a matter of logic or grammar, the language of the method claims did not impose a specific order on the performance of the method steps, and the specification did not directly or implicitly require a particular order). See also paragraph *>IV.<, below. **>When< an element is claimed using language falling under the scope of 35 U.S.C. 112, 6th paragraph (often broadly referred to as means or step plus function language)**, the specification must be consulted to determine the structure, material, or acts corresponding to the function recited in the claim. *In re Donaldson*, 16 F.3d 1189, 29 USPQ2d 1845 (Fed. Cir. 1994) (see MPEP § 2181- § 2186).

In *In re Zletz, supra,* the examiner and the Board had interpreted claims reading "normally solid polypropylene" and "normally solid polypropylene having a crystalline polypropylene content" as being limited to "normally solid linear high homopolymers of propylene which have a crystalline polypropylene content." The court ruled that limitations, not present in the claims, were improperly imported

from the specification. See also *In re Marosi,* 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) ("Claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest reasonable interpretation'." 710 F.2d at 802, 218 USPQ at 292 (quoting *In re Okuzawa,* 537 F.2d 545, 548, 190 USPQ 464, 466 (CCPA 1976)) (emphasis in original). The court looked to the specification to construe "essentially free of alkali metal" as including unavoidable levels of impurities but no more.). Compare *In re Weiss,* 989 F.2d 1202, 26 USPQ2d 1885 (Fed. Cir. 1993) (unpublished decision - cannot be cited as precedent) (The claim related to an athletic shoe with cleats that "break away at a preselected level of force" and thus prevent injury to the wearer. The examiner rejected the claims over prior art teaching athletic shoes with cleats not intended to break off and rationalized that the cleats would break away given a high enough force. The court reversed the rejection stating that when interpreting a claim term which is ambiguous, such as "a preselected level of force", we must look to the specification for the meaning ascribed to that term by the inventor." The specification had defined "preselected level of force" as that level of force at which the breaking away will prevent injury to the wearer during athletic exertion.**)

Appellants have argued the avidin-biotin affinity but have also deleted the same. Further

appellants argue that the same IRM compound complexes are not disclosed.

The examiner has given an obviousness rejection and dropped the 102 rejection.

The US patents Slade , Miller and Gerster teach the IRM compounds for the same use.
The Langler reference teaches the use of drug- macromolecular support complexes for drug delivery. I t also teaches a cancer treating drug with is covalently bonded to a macromolecule.
WO 2001/023067 Breuning and US 5078978 Tarbet both teach using the Si spacers and the Si support
It would have been obvious to one of skill in the art of drug delivery and would have known of these various drug delivery techniques of making drug –macromolecule complexes as given by Langer and hence would be motivated to make the complexes from the IRM compounds of the Slade , Gerster and Miller with the macromolecules and supports as disclosed by Langler in order to deliver it to the desired location or for administration, in other words “targeting" drugs to specific cells.
In view of KSR v Teleflex 2007, rationale it would certainly be obvious to try to make appellants complexes.
Applicants claims are broad and include any macromolecule and does not describe the spacer or the specific drug. See claim 1.

The claims are read in light of the specifications but the limitations of the specifications cannot be read into the claims..

Response regarding the Double Patenting:-

The examiner appreciated the appellants correcting the obvious typographical error and gave the correct US patent number on which the rejection should have made.

So it appears that the appellants understood the rejection , and had sufficient opportunity to reply.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections under 25 USC 103 and the ODP should be sustained.

Respectfully submitted,

/Rita J. Desai/

Primary Examiner, Art Unit 1625

Conferees:

/Janet L. Andres/

Supervisory Patent Examiner, Art Unit 1625

/Daniel M Sullivan/

Supervisory Patent Examiner, Art Unit 1621